REMARKS

Upon entry of this amendment, Claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35, and 56 are pending in the present application. Among them, Claims 2, 17-20, 36-55, and 57-68 are directed to non-elected invention, and are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope to all canceled claims in one or more future divisional or continuation applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

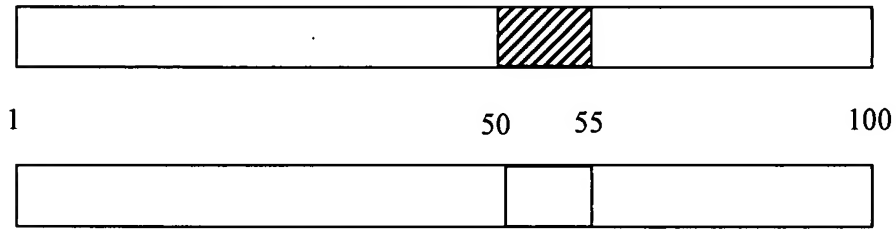
Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action continues to rely on a misinterpretation of Ginalski to reject the claims. In addition, in the last Office Action response, Applicants have argued that it is the overall sequence homology between the *entire* substituted recipient polypeptide and the *entire* wild-type polypeptide that should be compared, not the local sequence homology between the substituting (protease) *motif* and the substituted *motif*. Applicants note that the Office Action has not addressed this argument in the instant Office Action.

Thus, Applicants wish to reiterate that the key issue here is what Ginalski means "very close (sequence) homolog"? Applicants submit that it means overall sequence homology between the entire sequences of the *wild-type recipient polypeptide* and the *substituted recipient polypeptide*. In contrast, the Examiner interprets "very close (sequence) homolog" to mean local sequence homology between the *substituting protease motif* and the *substituted motif* (on the recipient polypeptide).

Merely to illustrate, in the following schematic drawing (not to scale), a 100-amino acid wild-type recipient polypeptide is represented by the large open bar at the bottom. If the spatially conserved protease motif (represented by the small hatched box) happens to have 6

amino acids, and happens to match a 6-amino acid stretch (*i.e.*, residues 50-55, represented by the small open box) of the wild-type recipient polypeptide, substituting the matching residues in the wild-type recipient polypeptide would result in a candidate recipient polypeptide with the conserved protease motif (represented by the large open bar with the small hatched box on the top).



The Examiner argues that Ginalski mandates a "very close (sequence) homology," while "the instant claims do not require any sequence homology between the amino acid residue set derived from a protease motif and the substituted amino acid residue set within said recipient polypeptide." Thus apparently, the Examiner is comparing local sequence homology between the small hatched box and the small open box between residues 50-55 on the recipient polypeptide.

This, however, is incorrect. The correct comparison for sequence homology should be between the entire wild-type recipient polypeptide (the large open bar at the bottom) with the entire substituted recipient polypeptide (the large open bar on the top). The Examiner's interpretation contradicts with the principal of Ginalski, because any substituting amino acids are *necessarily* different from the substituted amino acids (otherwise, there would be no substitution at all). For example, if only one amino acid is substituted, there is 0% sequence identity between the original amino acid and the substituted amino acid. But according to the Examiner's interpretation, Ginalski couldn't possibly be used for any structure prediction where, as here, there is only a single amino acid change. In fact, this rationale also applies to any other number of amino acid changes.

As a skilled artisan will appreciate, Ginalski relates to a molecular biology technique known as "homology modeling," in which protein structure is predicted based on protein sequence information. This method is generally quite accurate if protein A has a known

structure (such as the wild-type recipient polypeptide), and if protein B has "very close (sequence) homology" with protein A (such as the substituted recipient polypeptide, which shares at least 94% sequence identity with the wild-type protein). This is because minor amino acid sequence changes generally do not result in dramatic disruption of the overall protein structure. Thus if residues 50-55 in the wild-type protein is substituted by a conserved protease motif (the hatched box), the overall structure should not be affected, especially when the claim requires that the conserved protease motif (the hatched box) "have a geometric relationship that matches the spatially conserved geometry" of the wild-type motif (the small open box).

This is much like a laptop computer with a swappable bay, which may accept different swappable devices such as an extra battery, a DVD drive, a floppy disk drive, or a hard disk, *etc.* Although these different devices may be completely different with respect to their structures and functions, as long as the external geometric shapes of these swappable devices are the same, any one of such devices may be inserted into a single opening on the laptop computer, thus imparting dramatically different functionality to the laptop computer.

Simlarly, even if the sequence of the 6 residues in the small hatched box is 100% different from the sequence of the 6 residues in the original white open box, so long as the overall geometric shape of the conserved protease motif matches that of the to-be-replaced motif, the substituted recipient polypeptide is expected to maintain the same three-dimensional folding of the wild-type protein, because the substituted recipient polypeptide (with the small hatched box) is still 94% identical to the wild-type recipient polypeptide (with the small open box). Because of the high sequence identity (*i.e.*, 94% identical), Ginalski would predict that the overall structure of the substituted and wold-type recipient polypeptides are largely the same.

The Examiner also asserts that "... prediction of structure and activity in polypeptides can be reliably accomplished only if very close homologs of known structures are available and if said homologs further share high degrees of structural, sequence and activity similarity."

While Ginalski may have referred to the relationship between *structure* and *sequence*, Applicants are unable to find where in Ginalski is the reference to "activity similarity"

between the original set of amino acids in the recipient polypeptide and the set of residues substituted into the recipient polypeptide. Clarification is respectfully requested.

The Examiner appears to be concerned that there is no limitation recited in the claims that limit the number of amino acid residues substituted into a recipient polypeptide.

To advance prosecution, Applicants have incorporated the subject matter of Claims 14 and 34 into the independent claims to recite the range of residue numbers within the spatially conserved motif. As a result, Claims 14 and 34 are canceled without prejudice. Applicants submit that this amendment is made solely to advance prosecution in order to protect commercially important embodiments of the presently claimed invention. It should not be construded as Applicants' acquiescing in the reasoning of the rejection. Applicants reserve the right to prosecute claims of identical or similar scope to the claims before this amendment.

The Examiner also seems to be concerned that "the instant claimed method requires only a geometric relationship that matches a conserved geometry." The Examiner appears to consider this requirement as contrasting the prior art emphasis on sequence and structure similarity.

Applicants submit that this concern is unfounded, partly because it is based on the incorrect assumption that only similar sequences can have similar structures. In fact, many polypeptides with very different sequences can fold into quite similar three-dimensional structures. For example, Metcalf *et al.* (*Nature* **325**: 84-86, 1987) reported that two variant surface glycoproteins (VSG) of a blood parasite (*Trypanosoma Brucei*) has "strikingly similar" three-dimentional structures based on X-ray crystallography study, yet "most known VSG sequences show little similarity of primary (amino acid) sequence" (abstract of Metcalf).

As a skilled artisan will appreciate, high sequence homology usually portends high structural similarity. This, however, does not mean that dissimilar sequences cannot have similar structures. In the context of the claimed invention, what is important is a matching structure between the protease motif and the to-be-replaced motif, so that the overall structure

of the substituted recipient polypeptide is conserved. It is probably even better if the substituted protease motif can have different sequence (compared to the substituted motif), so that a new functionality is created on the resulting recipient polypeptide, so long as the overall structure of the substituted recipient polypeptide is conserved. Using the swappable bay laptop analogy, all that is required is a conserved geometric shape shared by the different swappable devices.

In summary, Ginalski actually supports the enablement of the claimed invention, because the overall sequence identity between the substituted and wild-type recipient polypeptides are high. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Specifically, regarding Claims 1 and 21 (and their dependent claims), the Office Action argues that in the *in silico* embodiment, the resulting recipient polypeptide "embodies only a computer representation and it is unclear how a physical step drawn to testing for catalytic activity can be performed on a computer representation of said recipient polypeptide."

To further clarify the subject matter claimed, Applicants have amended Claims 1 and 21 to recite in step (d) "expressing and testing" the substituted recipient polypeptide. This is supported by page 11, first full paragraph of the specification.

The amended claims unambiguously recite a physical transformation step that requires expressing the subsituted recipient polypeptide as a real world polypeptide, and testing for its protease activity. Thus even in the *in silico* embodiment, a substituted recipient polypeptide created in the virtual world will need to be expressed and tested in the real world for its activity.

The Office Action also rejects Claims 1, 21, and 56 for reciting "catalytic activity," because it is allegedly unclear if the recited "catalytic activity" refers only to protease activity or some other activities.

Applicants have amended the claims to replace "catalitic activity" with "protease activity" to overcome this rejection.

Therefore, the metes and bounds of the claimed invention is unambiguously defined by the amended claims. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim rejections under 35 U.S.C. § 101

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. § 101, because the claimed invention is allegedly directed to non-statutory subject matter. Specifically, the Office Action argues that in the *in silico* embodiment, the claimed invention still does not include a physical transformation step. The Office Action further argues that the claimed *in silico* embodiment fails to produce a tangible result because the claims allegedly lack a limitation to somehow display the modeling results.

While not acquiescing in the reasoning of the Office Action and solely to advance prosecution, Applicants have amended independent Claims 1, 21, and 56 to unambiguously recite in step (d) a physical transformation step, *i.e.*, expressing and testing the engineered polypeptides for protease activity, thereby obviating the non-statutory subject matter rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicants believe no additional fee other than the THREE-month extension fee is due with this response. However, if any additional fee is due in connection with the filing of this response, please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P01-002**.

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Respectfully submitted,

By_____

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